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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,929	05/04/2000	Christoph Kessler	4817/OP	4989

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EXAMINER	
SISSON, BRADLEY L	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,929	KESSLER ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/11/02, 4/11/03, 10/9/03, 12/9/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/6/02 & 10/9/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Location of Application

1. The location of the subject application has changed. The subject application is now located in Group 1630, Art Unit 1634.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of claims 1 with the added limitations of the nucleic acid being derived from HCV RNA found in human plasma, does not reasonably provide enablement for the detection of any number of nucleic acid sequences simultaneously nor does the specification enable the use of any set of conditions such that non-specific hybridization reaction products are realized, nor does the specification enable the use of primers such that amplificates of any length are produced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004

(Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

Amount of Direction Provided

4. The amount of guidance provided is extremely limited, and then it is directed to the detection of HCV RNA isolated from human plasma.

The Presence or Absence of Working Examples

5. The specification provides 5 examples:

- Example 1, pages 47-50; Detection of HCV from human blood;
- Example 2, pages 50-51, Determination of he analytical sensitivity on the basis of an RNA standard;
- Example 3, page 52, Examination of the specificity of the HCV assay;

- Example 4, page 53, Examination of the Probe Specificity (conditions under which the hybridization assay was preformed are not disclosed); and
- Example 5, page 54, Detection of HCV using Alternative Primers (prophetic).

The State of the Prior Art

6. The state of the prior art has advanced to the point where he art now recognizes that there are a number of issues confronting hybridization reactions and that they need to be properly addressed in order to enable a method predicated upon such method steps. As set forth in Carrico, (US Patent 5,200,313) the extent and specificity of hybridization is affected by the following principal conditions:

1. The purity of the nucleic acid preparation.

2. Base compositions of the probe - G-C base pairs will exhibit greater thermal stability than A-T or A-U base pairs. Thus, hybridizations involving higher G-C content will be stable at higher temperatures.

3. Length of homologous base sequences- Any short sequence of bases (e.g., less than 6 bases), has a high degree of probability of being present in many nucleic acids. Thus, little or no specificity can be attained in hybridizations involving such short sequences. From a practical standpoint, a homologous probe sequence will often be between 300 and 1000 nucleotides.

4. Ionic strength- The rate of reannealing increases as the ionic strength of the incubation solution increases. Thermal stability of hybrids also increases.

5. Incubation temperature- Optimal reannealing occurs at a temperature about 25 - 30 °C below the melting temperature for a given duplex. Incubation at temperatures significantly below the optimum allows less related base sequences to hybridize.

6. Nucleic acid concentration and incubation time- Normally, to drive the reaction towards hybridization, one of the hybridizable sample nucleic acid or probe nucleic acid will be present in excess, usually 100 fold excess or greater.

7. Denaturing reagents- The presence of hydrogen bond-disrupting agents, such as formaldehyde and urea, increases the stringency of hybridization.

8. Incubation- The longer the incubation time, the more complete will be the hybridization.

9. Volume exclusion agents- The presence of these agents, as exemplified by dextran and dextran sulfate, are thought to increase the effective concentrations of the hybridizing elements thereby increasing the rate of resulting hybridizations.

7. Further, subjecting the resultant hybridization product to repeated washes or rinses in heated solutions will remove non-hybridized probe. The use of solutions of decreasing ionic strength, and increasing temperature, e.g., 0.1X SSC for 30 minutes at 65 °C, will, with increasing effectiveness, remove non-fully complementary hybridization products.

8. The art has also advanced to the point where it is now recognized that there is a limit to which primers can be synthesized and still retain high fidelity to the nucleotide composition. US Patent 5,858,671 (Jones et al.), column 40, teaches the existence of an inherent obstacle in synthesizing oligonucleotide arrays. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant

levels. For example, during oligonucleotide synthesis of a 70-mer, requiring 69 couplings, 1 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ($0.99^{69}= 0.50$)." In the present case, the claims encompass the use of probes and primers that are the result of an infinite number of couplings, as well as the production f amplificates that result from up to 100 couplings, not just 69 as described above by Jones et al.

Relative skill in the art

9. The relative skill of those in the art that is most closely associated with the claimed invention is high, on par with those that hold a Ph.D. in biochemistry.

Nature of the Invention; Breadth of Scope of the Claims; and Quantity of Experimentation Necessary

10. The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

11. As presently worded, the claimed methods fairly encompass the detection of nucleic acid sequences that are indicative of any condition, be it pathological, infection, or predisposition. Said method claims have also been interpreted as encompassing the detection of such nucleic acid sequences where there is but a single nucleotide difference between amplificates, as well as

the production of virtually an infinite number of different amplificates where the templates are from different, highly unrelated organisms, yet the size of the amplificates, and the label used are similar and/or identical.

12. A review of the disclosure fails to identify where applicant has set forth the probes and primers required to practice the claimed method where any number and combination of nucleic acids are to be detected.

13. It is noted with particularity that the methods stipulate that the primers need only to be "essentially complementary." A review of the specification fails to find a definition that limits the scope of what can be construed as being "essentially complementary." Accordingly, the claims have been interpreted as encompassing the use of primers that are significantly non-complementary to the template. Indeed, the method of claims 11 and 12 require that one use primers that are "not specific for the nucleic acid to be detected." Also, a claim 13 requires that one use of probe that is not specific for the nucleic aid to be detected.

14. In view of the claim being directed to the detection of specific nucleic acids wherein the nucleic acid is associated with physiological and chemical states of an individual (e.g., cancer, intelligence, obesity, predisposition to developing any condition or trait, blood pressure, regulation of Na levels, etc.), and requires that primers and probes be non-specific for the amplificates, be there any number and combination of amplificates, the invention is directed to a highly unpredictable area of art.

15. As seen above, the specification provides very limited examples yet the claims encompass a much broader scope for which starting materials (primers and probes) have not been provided and procedures for interpreting the results have not been disclosed. While

argument has been raised that it is within the level of skill in the art to make probes, such argument has not been found persuasive as the claimed methods is not drawn to a method of making probes, but rather, is drawn to a method of using probes and primers that must already exist. A review of the disclosure fails to find where applicant has provided the requisite starting materials in order for the full scope of the invention be practiced.

16. While there is no *per se* requirement for examples to be provided, it is well settled that the level of disclosure varies inversely with the predictability of the art. Such fully enabling disclosure is not found within the four corners of the instant application. The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (starting, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling

> disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skill in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

17. Argument is presented at page 9 of the response of 11 July 2002 where attention is directed to pages 41-42 of the disclosure. In particular, applicant asserts that the disclosure enables the embodiments where primers and probes are nonspecific, yet meaningful results are still obtained.

18. The above argument, including pages 41-42 of the specification, has been fully considered and has not been found persuasive towards the withdrawal of the rejection. While the specification states:

> Unspecific nucleic acid amplification products are not detected on the nuclei acid if the specific binding sequence for the probe is absent.

19. It is noted, however that the claimed methods do not require the use of only "specific" binding probes. Indeed, claim 1 only requires that the probe bind in any manner to a region B, which is located between regions A and C. Furthermore, claim 13 demands that the probe be nonspecific and claims 11-12 require that the primers be non-specific. It stands to reason, therefore, that if the primers and probes are non-specific, non-specific signals are to be detected. Even if a specific and desired product is to be produced, the specification does not set forth a reproducible procedure whereby a useful signal can be discriminated from a useless signal.

20. In view of the breadth of the claims, the unpredictable nature of the invention, the limited guidance provided, skilled artisan s would have to resort to trial-and-error experimentation in

order to develop suitable primers and probes, as well as methods that would allow for their use, be it singly or in a highly multiplex manner where highly divergent nucleic acids are detected yet have the same size and label. Such efforts would be conducted with little if any reasonable expectation that the full scope of the claims could be practiced. The level of experimentation required on the part of those skilled in the relevant art clearly constitutes undue experimentation.

21. In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are not enabled by the disclosure. Accordingly, claims 1-19 remain rejected under 35 USC 112, first paragraph.

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 1-15 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

24. Claim 1 is indefinite with respect to what constitutes "essentially complementary." Claims 2-15, which depend from said claim 1, fail to overcome this issue and are similarly rejected.

25. Acknowledgement is made of applicant's traversal of this rejection and having directed attention to page 25 of the disclosure (see page 10 of response received July 11, 2002). Applicant's argument and the cited portion of the specification have been fully considered and

have not been found persuasive towards the withdrawal of the rejection, as the definition provided in the specification is non-limiting. More particularly, while page 25 of the specification does provide an example of how the term could be interpreted, the phrase is not limited to only that example. Accordingly, the metes and bounds of the claims cannot be readily determined and as such, claims 1-15 remain rejected under 35 USC 112, second paragraph.

Double Patenting

26. Claims 16-19 of this application conflict with claims 16-19 of Application No. 09/530,746. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

27. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefore ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

28. A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

29. Claims 16-19 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 16-19 of copending Application No. 09/530,746. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

30. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

31. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

32. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

33. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/530,746. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to method for the detection of nucleic acids where a target nucleic acid is amplified through the use of two primers and the amplificates are detected by hybridizing a probe to said amplificates where the region that the probe binds does not overlap with the sequence to which either primer binds.

34. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

35. Claims 1, 2, 4, 5, 8, and 11-14 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of

copending Application No. 09/530,747. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to method for the detection of nucleic acids where a target nucleic acid is amplified through the use of two primers and the amplificates are detected by hybridizing a probe to said amplificates where the region that the probe binds does not overlap with the sequence to which either primer binds.

36. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

37. Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-22 of copending Application No. 10/322,138. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to method for the detection of nucleic acids where a target nucleic acid is amplified through the use of two primers and the amplificates are detected by hybridizing a probe to said amplificates where the region that the probe binds does not overlap with the sequence to which either primer binds.

38. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

39. Rejections and/or objections that appeared in the prior Office action and not repeated hereinabove have been withdrawn.

40. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

41. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

42. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is 571-272-0751. The examiner can normally be reached on Monday through Thursday from 6:30 AM to 5 PM.

43. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

44. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR

system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS
5/14/2004